

Claims

Sub A
1. A method to identify a compound which will effect apoptosis selectively in tumors, which method comprises assessing a candidate compound for its ability to inhibit mitochondrial ATP synthase, whereby a compound which is able to inhibit said synthase is identified as a compound that will selectively effect apoptosis in tumors.

2. The method of claim 1 wherein said assessing is by assessing the ATPase activity of said synthase.

3. The method of claim 2 wherein said ATP synthase is obtained from yeast.

4. The method of claim 1 wherein said candidate compound is an analog of apoptolidin.

5. The method of claim 4 wherein said analog is produced from a modified form of the synthase for apoptolidin or of its tailoring enzymes.

6. A method to enhance the ability of a compound that inhibits mitochondrial ATP synthase to effect apoptosis of tumor cells which method comprises contacting said tumor cells with at least one agent which suppresses the anaerobic degradation of glucose in said cells.

7. The method of claim 6 wherein said agent is 2-deoxyglucose or oxamate.

8. A method to treat solid tumors in a subject which method comprises administering to a subject in need of such treatment an amount of an inhibitor of mitochondrial ATP synthase effective to cause apoptosis in said tumor.

9. The method of claim 8 wherein said compound is identified by the method of claim 1.

10. The method of claim 8 wherein said compound is an analog of apoptolidin.

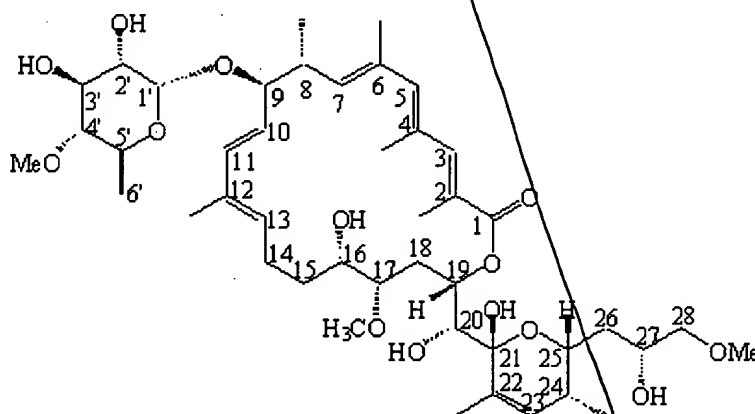
11. The method of claim 10 wherein said analog is produced from a modified form of the synthase for apoptolidin or of its tailoring enzymes.

12. The method of claim 8 which further comprises administering to said subject an amount of an agent which suppresses the anaerobic degradation of glucose in an amount effective to enhance the cytotoxicity of the inhibitor of mitochondrial ATP synthase.

13. A method to enhance the treatment of solid tumors in a subject by an inhibitor of mitochondrial ATP synthase, which method comprises administering to a subject that comprises said tumor, an amount of an agent effective to suppress the anaerobic degradation of glucose in said tumor.

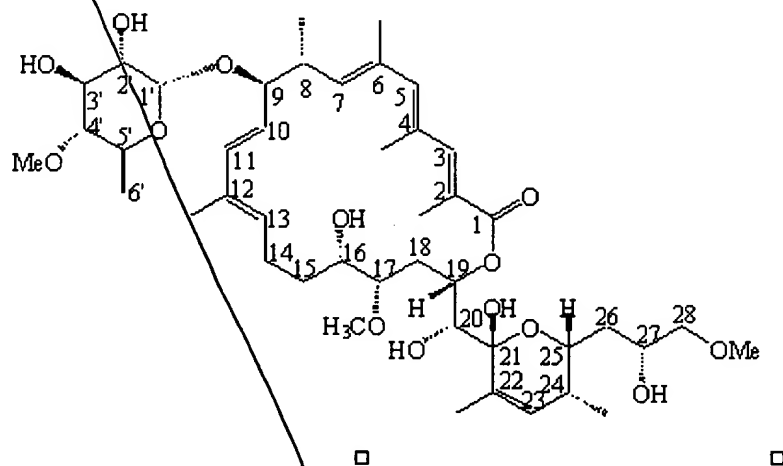
14. The method of claim 13 wherein said inhibitor of ATP synthase is apoptolidin or an analog thereof.

15. The method of claim 13 wherein said inhibitor of ATP synthase is a compound of the formula

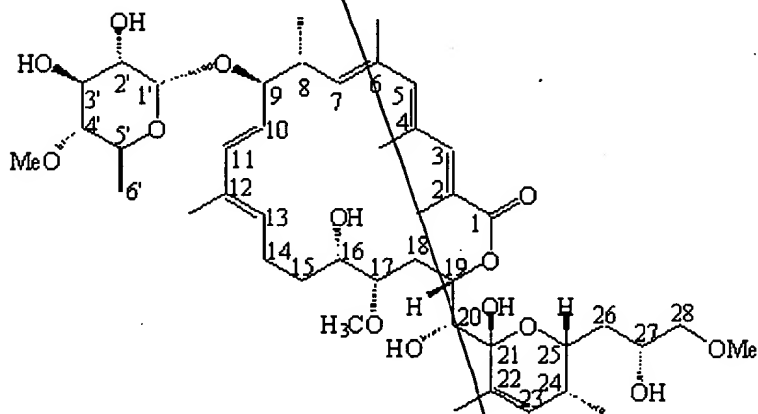


including the stereoisomeric forms, ethers (1-2C) and esters (1-6C) thereof.

16. The method of claim 15 wherein said inhibitor of ATP synthase is a compound of the formula

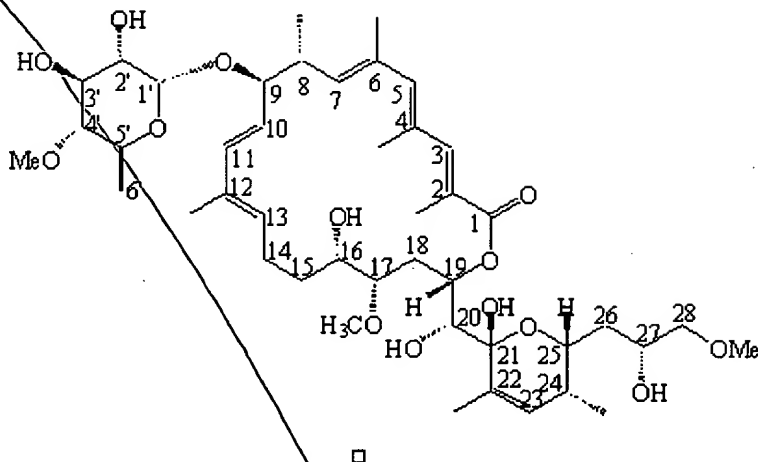


17. A compound of the formula



and the stereoisomeric forms, ethers (1-2C) and esters (1-6C) thereof.

18. The compound of claim 17 which is



19. A pharmaceutical composition comprising as active ingredient the compound of claim 17.

20. A pharmaceutical composition comprising as active ingredient the compound of claim 18.

21. A method to prepare the compound of claim 17 which method comprises treating apoptolidin with an organic or inorganic acid in the presence of alcohol at ambient temperature for a time sufficient to effect the conversion of apoptolidin to the compound of formula 1 and optionally converting said compound of formula 1 to the ether or ester form.